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ARE FUNCTION AND FUNCTIONAL STIMULUS FACTORS IN PRODUCING AND PRESERVING MORPHOLOGICAL STRUCTURE?

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Since the days of Lamarck the attempt has often been made of explaining the genesis of the morphological structure of organisms through the theory of adaptation. A special form of this theory is that of "functional adaptation" which was formulated under this name by Wilhelm Roux about 1880, and was later elaborated by that investigator in an extremely extensive and thorough manner.

The most striking organic structures are those which like the bones seem to be constructed on a definitely purposeful plan, offering the largest amount of strength with the smallest amount of material. Other organs, such as the muscles, increase in size as a result of increased function. Roux named this phenomenon "functional adaptation," while the structures underlying this principle he described as "functional structures." He made a number of exceedingly careful anatomical studies of such "functional structures." Endeavoring to explain the genesis of such seemingly purposeful structures from a purely mechanical standpoint, he found that they possessed exactly that construction which was to be expected from a mathematical calculation based on the principle of functional adaptation.

In order to make clear the development of functional adaptation, Roux fell back upon the most primitive particles of living matter. In his opinion some of these particles have been adapted to respond to functional stimuli, that is, they show a greater tendency to proliferate in the presence of functional stimuli than in their absence. Thus, those elements which were subjected to stimuli soon predominated over those which were not thus exposed.

If functional structures consisted of such particles, they would

show the following characteristics: first, enlargement (functional hypertrophy) with increased stimulus; second, atrophy from inactivity upon cessation of the stimulus; third, regeneration of organs of functional structure to the condition of the original structure would only be possible in the presence of function and functional stimuli (functional regeneration); and fourth, the successful transplantation of functional structures would only be conceivable if after transplantation the organs involved were supplied with an appropriate amount of functional stimulus. The principles, therefore, necessary for an acceptance of the theory of functional adaptation are: functional hypertrophy, atrophy from inactivity, functional regeneration, and functional transplantation. (Various other factors which are similarly instrumental in this connection will be dwelt upon more extensively in a subsequent paper.) Should it now appear that these essential principles in so-called functional structures are non-existent, the theory of adaptation would then fail to adequately account for so-called functional structures.

Before giving the results of my experiments I wish to say a few words about the general value of Roux's theory of functional adaptation.

This theory at a cursory glance has many merits, and at the time when first introduced by Roux it marked a substantial advance, inasmuch as it showed that it was possible to produce highly purposeful structures through the influence of purely mechanical principles. On this basis the theory has become a material factor in connection with the investigations and studies of many workers in the realms of pathology and physiology.

Roux's theory, however, has great disadvantages, one of which is its extremely complicated and extensive terminology. It is probably owing to the extreme obscurity of the doctrine that comparatively few investigators, apart from the originator of the theory, have familiarized themselves with it and fully understood its principles. As a result of this practically the only valuable work along this line has been carried on under the direct control of Roux himself, while in contrast with the comparatively scanty publications emanating from Roux's laboratory an amazingly voluminous mass of literature has been supplied

by outside writers, all of whom were under the impression that they were contributing something to Roux's theory, but who in reality had hardly grasped more than a few but imperfectly comprehended terms connected with the essential problem. These for the most part misleading publications have caused more error than progress in experimental work. I shall endeavor to prove this point in a subsequent and more extensive article.

A second disadvantage of Roux's theory is the fact that the extent of the field in which it is applicable becomes more and more restricted with the increasing number of "experimental" investigations bearing directly upon this problem. Consequently, in course of time the phenomena which are not in harmony with this principle of functional adaptation increase in number, although they may be explained, together with other phenomena, from another point of view.

However, by far the weightiest objection to the theory is that it threatens to become more and more of a stumbling block to workers who are setting out to investigate the problems of organic and inorganic life from a common viewpoint. Nowadays theories such as that of function and functional stimulus can hardly be reconciled with a chemico-physical view of the life processes; for the whole underlying principle of the theory of adaptation does not lend itself to methods of measurement. For this reason a detailed revision of the theory of functional adaptation has become necessary and will be published in a later communication.

In the present paper I shall report on the results of a few experiments which I began five years ago with the above mentioned object in view. As they are at the present moment sufficiently advanced to allow of a survey of the whole point at issue and to show that they are qualified to throw some light on the problem of functional adaptation, a preliminary discussion of these experiments may be warranted.

The experiments in question were performed on the transplanted eye of *Salamandra maculosa*. The eye of a larva was transplanted into the neck of another larva, where after a few days' partial or complete disappearance of the retina resulted, ending finally in complete degeneration. *The remarkable fact*

was that this degeneration was followed later by a complete regeneration of the transplanted eye, even in the dark.

My experiments were conducted with the following considerations in view. The retina is one of those structures which according to Roux's definition should be called a functional structure. But in accepting this definition one need not necessarily assume that these structures are the result of functional stimulus, for such structures may have been predetermined in the embryonic stage. They develop independently of functional stimulus until they reach the third period—the so-called functional period.¹ Functional structures can only exist during this period if they are supplied with a sufficient amount of functional stimulus; otherwise they undergo atrophy through inactivity. From Roux's point of view it would appear probable that the morphogenesis of the eye of *Urodela* is only partially determined by inheritance, and in accordance with this determination it would reach the same stage of development as that attained by *Proteus anguineus*. The further development of the eye, comprising the formation of the rods and cones, that is the true functional parts, would be brought about by the penetration of the rays of light through the skin of the salamander, to its ovaries, and would therefore be the outcome of functional stimulus. Secerov² asserts that the skin of *Salamandra maculosa* permits of the penetration of approximately 1/173 of the quantity of light in which the animal lives.

The eyes of *Proteus*, which inhabits dark caves, must therefore remain in the primitive *Proteus* stage, according to the statement of Kammerer,³ who believes he has demonstrated that further differentiation can only occur if *Proteus* be kept in the light. Thus, he ascribes the process of full differentiation

¹ See, for example, Roux, "Die Entwicklungsmechanik, ein neuer Zweig der biologischen Wissenschaft," Vorträge und Aufs. über Entwickl.-Mech. d. Organismen. 1905, Heft I., p. 94, note 11. Also Roux, "Die vier Hauptperioden der Ontogenese, sowie das doppelte Bestimmte sein der organischen Gestaltungen," *Mitteilung der naturforschenden Gesellschaft*, Halle a.d.S., 1911, I., p. 1.

² Secerov, S., "Die Umwelt des Keimplasmas. II. Der Lichtgenus im Salamandra-Körper," *Arch. f. Entwicklungsm.*, 1912, XXXIII., 682.

³ Kammerer, P., "Experimente über Fortpflanzung, Farbe, Augen und Körperreduktion bei *Proteus anguineus* Laur. Zgl. Vererbung erzwungener Farbveränderungen." III. Mitteil., *Arch. f. Entwicklungsm.*, 1912, XXXIII., 349.

of the eye in the case of several *Proteus* which were kept in the light, directly to the influence of function, and Roux is apparently of the same opinion. This point will be discussed by the writer in a later paper.

My own observations on the transplanted eye of *Salamandra* soon convinced me that this case lends itself very well for the test of the theory of functional adaptation.

First of all I severed the optic nerve, a procedure which according to general opinion should induce permanent degeneration of the retina as a result of the eye becoming isolated from the brain. In all previous operations of this nature, where, however, the eye remained in its normal position, a reunion of the amputated stumps of the nerve took place, so that it was natural to suppose that the re-connection of the eye with the brain brought about regeneration of the retina. In my own experiments I obviated the possibility of such subsequent reunion of the eye with the brain by transplanting the eye to an abnormal position (in the neck of the salamander). But regeneration took place in spite of this fact. The point of chief interest, however, is the fact that by means of this operative measure, which, as has been demonstrated in 95 per cent. of the cases, excludes reunion of the eye with the central nervous system, the eye is permanently deprived of functional power.

It is thus obvious that in these eyes no function was possible and the experiment therefore shows that a whole series of phenomena, hitherto designated as cases of functional adaptation, require a different explanation. We will now discuss these phenomena in greater detail.

I. In about a week after transplantation of the eye into the neck of the salamander the retina had degenerated to such an extent that in many cases only the peripheral part of the retina, which was not differentiated in layers, had survived.¹ But in spite of its permanent isolation from the brain and despite the fact that the eye was permanently deprived of function, the retina from this time on began to show signs of regeneration and the transplanted eye began to receive a progressively im-

¹ E. Uhlenhuth, "Die Transplantation des Amphibienauges," *Arch. f. Entwicklungsm.*, 1912, XXXIII.

proved supply of blood, so that in a comparatively short time (from 4 to 6 weeks) it had regained a perfectly normal structure.

II. This regeneration of the transplanted eye even takes place when the organ is deprived of functional stimulus by light. A series of salamanders operated on in the above-described manner, were placed in a dark room where neither red nor white light could penetrate to their eyes; but in spite of this fact the transplanted eyes regenerated and developed a normal retina.

These experiments show that the "quality" of this process, namely, regeneration as such, is independent of any sort of functional influence. We are here dealing with a case of simple regeneration, such as is found in many organs, not with *functional* regeneration, such as we might expect to find in so-called functional structures. Of course this fact does not warrant us in entirely rejecting the theory of functional adaptation, for the possibility must not be ignored that although regeneration occurs in eyes treated in this way as a result of the agency of certain other factors, nevertheless degeneration brought about by atrophy through inactivity might follow later, as a result of the permanent lack of function and functional stimulus, a possibility which would be expected to arise according to Roux's theory.

III. But secondary degeneration as a result of atrophy from inactivity failed to occur in my experiments, even when the eyes were permanently deprived of function, as occurred in the "light" series.

IV. Degeneration similarly failed to occur in the transplanted eyes which were permanently deprived of both function and functional stimulus, namely in the "dark" series. These eyes, although severed from the brain and in permanent darkness, grew and metamorphosed simultaneously with the normal eyes of the hosts.¹

Up to the present time I have had at my disposal preparations of eyes of the "dark" series which were preserved 15½ months after transplantation; at that time the hosts were about 21

¹ E. Uhlenhuth, "Die synchrone Metamorphose transplantiertter Salamander-
augen (Zugleich, Die Transplantation des Amphibienauges II. Mitteil.) *Arch.
f. Entwicklunqsm.*, April, 1913, XXXVI., 211.

months old, and all the structures, with the exception of the sex organs, were perfectly developed. The retinas of these transplanted eyes were found to be normal in every detail.

In addition to the above I have a preparation of an eye of the "light" series, which was preserved 3 1/4 years after transplantation, at which time the sex organs were also fully developed. According to Roux the eye of an amphibian should by that time already have entered the functional period, as is believed to have been proved in the case of the eye of the *Proteus*. Nevertheless, the old transplanted eyes were also found to be normal, and the functional parts of the retina, viz., the rods and cones, were present and well developed.

The above results, namely, the permanent preservation in a normal condition of transplanted eyes, prove beyond any doubt that the so-called functional structures of the eye do not undergo atrophy through inactivity, even if they are kept under extremely unfavorable conditions and are deprived of all function and functional stimulus.

This fact alone is sufficient to show that atrophy from inactivity, which is one of the fundamental postulates of Roux's theory, is by no means a phenomenon of general occurrence which takes place in all so-called functional structures permanently deprived of functional stimulus, as was supposed to be the case.

As far as regeneration is concerned, the experiments mentioned above only serve to show that regeneration in itself is independent of function and functional stimulus.

V. I am, moreover, able to demonstrate that the "quantity" of the regenerative process in the eyes, viz., the rapidity of this regeneration are not influenced by functional stimulus, viz., light.

A certain number of animals (260 in all) of both the light and the dark series were preserved at certain intervals of time and the transplanted eyes were cut in sections. Eyes preserved at equal intervals of time were then compared with each other. It was found that the transplanted eyes of the same series which had lived on the host for the same period of time may show considerable differences in the rapidity with which they undergo regeneration, even if they are subjected to equal conditions

as far as functional stimulus is concerned. These differences must therefore be caused by other non-specific factors. In order to ascertain how far-reaching is the influence of light, it was necessary to determine the average rapidity of regeneration in every group of eyes of the same series and make a curve for each series. Although these curves are not yet completed, the results thus far obtained show no differences between light and dark series at all. Even the quantity of the regeneration is therefore uninfluenced by light.

From the above data we must draw the following conclusions: *Functional adaptation plays no part either in transplantation or in regeneration of the retina; nor is it a factor which determines either the quality or the quantity of these processes.*

This, of course, does not mean that regeneration or transplantation of the eye cannot be influenced at all by chemical or physical factors. On the contrary, as is shown by the differences between transplanted eyes of the same series, examined at equal intervals of time after transplantation, the quantity of regenerative processes, viz., the rapidity of regeneration are subject to variation by one or more factors. The point of importance is the fact that these factors are not connected with the specific functional stimulus, viz., light. Apparently they are the same factors which also affect the rapidity of the regenerative process of other organs. The factor concerned is probably the length of time since circulation in the transplanted eye was reëstablished.

Hitherto the regeneration of the retina has been considered as being different from the regeneration of the bones. It was supposed that a bone could only regenerate its architectural structure if in use, otherwise the result would not be a normal bone but a disorderly bony mass.

Aug. Bier,¹ however, has shown that even the bones do not regenerate as a mere indefinite mass of bone if kept without functional stimulus, but that on the contrary, in the absence of any such stimulus, they resume their original functional structure to the minutest details. In certain experiments a considerable part of a human tibia was removed. Although these

¹ Aug. Bier, "Beobachtungen über Knochenregeneration," *Arch. f. klin. Chir.*, Dec. 1912, c, 91.

bones were not exposed to any function, the tibiae after a certain length of time assumed their normal shape and structure, but only if they were supplied with nourishment in a proper way, and if sufficient space was left for them to regenerate the missing part.

The same is true of the tendons. H. Triepel¹ showed that the tendo Achillis of a cat can regenerate only tendon tissue, irrespective of the presence or absence of functional stimuli.

Our own experiments now prove the same principle also in the case of the eye of *Salamandra maculosa*; this organ regenerates its functional structures in the absence of functional stimulus, and furthermore it retains its structure permanently, despite the permanent absence of functional stimulus. For a long time it was believed that a bone only regenerated a structureless mass of callus in the absence of function, and according to this theory it would be assumed that an eye if once degenerated would in the absence of light regenerate undifferentiated retina cells, such as we find in the normal *Proteus* eye. Nevertheless, both eye and bone regenerate the normal and fully differentiated structure, even in the absence of functional stimulus.

We have seen that in my experiments the velocity of the process of regeneration was not influenced by function; and even if this had been the case it could not be used as a proof in favor of functional adaptation. There are a number of well known morphogenetic processes, the rapidity of which can be accelerated by light, although light bears no relation to the function of the developing organ, that is to say, is not a functional stimulus. The most striking experiments made in this connection are those of J. Loeb,² in which he showed that the regeneration of the hydrants of *Eudendrium* is impossible in the absence of light. Nevertheless, we cannot call this a case of functional adaptation, because here light is obviously not a functional stimulus. On the other hand, development of the eyes of fish embryos cannot be prevented by the exclusion of the func-

¹ Triepel, H., "Selbstständige Neubildung einer Achillessehne," *Arch. f. Entwicklungsm.*, Aug., 1913, XXXVII., 278.

² Loeb, J., "Über den Einfluss des Lichtes auf die Organbildung bei Tieren," *Pflügers Arch.*, April, 1896, LXIII., 273.

tional stimulus. But it is incorrect to ascribe this fact to the assumption that heredity may have fixed this character so far that development of an eye now occurs in the absence of light. For Loeb¹ has shown that it is very easy to prevent the development of these eyes by a number of different means, such as lack of oxygen, which is a non-specific, non-functional factor. Moreover, it is not necessary to point out that the influence of light on a photographic plate has never been considered to be a case of functional adaptation, although the sensitiveness of the plate to light is just as much response to a physical factor as is the regeneration of *Eudendrium* or as might be the variation in the rapidity of eye-regeneration which although not found in our experiments, might possibly have occurred.

The theory of functional adaptation complicates instead of simplifying the problem. What we should emphasize is not the fact that the result of the response to light is different in the case of *Eudendrium* from what it is in the case of the regenerated eye or of the photographic plate, but the fact that these three phenomena all possess a common basis. It is obvious that all three are governed by the same laws, with which we are familiar from our knowledge of physics and chemistry; but these laws are free from such terms as function, functional stimulus, or any other stimulus, or the principle of adaptation. In order, therefore, to obtain a fertile method for attacking the problems confronting us we must constantly bear in mind the fact that the same laws expressed in the same terms can explain both organic and inorganic phenomena.

¹ Loeb, J., "Heredity in Heterogeneous Hybrids," *Jour. of Morphol.*, March, 1912, XXIII., 1.